UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/515,984	07/06/2005	Carl-Fr Coester	FZ002-US	6317

24222 7590 05/21/2008

Vern Maine & Associates
100 MAIN STREET
P O BOX 3445
NASHUA, NH 03061-3445

EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/515,984	COESTER, CARL-FR	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-42* is/are pending in the application.

4a) Of the above claim(s) *40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to Applicant's arguments submitted on 02/22/2008. Claims 32-42 are pending in the applications, with claims 40-42 having being withdrawn. Accordingly, claims 32- 39 are being examined on the merits herein.

Receipt of the certified translation of German application No. 102 23 254.7 is acknowledged and has been entered. As a result the new priority date of the instant application is May 24, 2002.

Applicant's arguments against the 35 USC 103(a) rejection of claims 32-38 over Nelson et al. in view of FDA glossary terms or Van Walraven has been fully considered and is found persuasive. Indeed, the Nelson reference is a continuation-in part of application 10/192,414, which is a continuation-in-part of U.S. Patent 6,417,177 which claims priority to provisional application 60/479,748, filed June 19, 2003. Consequently, Nelson is unavailable as prior art over claims 32-38. Moreover, in light of applicant's claim to German application No. 102 23 254.7, whose priority is May 24, 2002, Nelson is unavailable as prior art. Consequently, the rejection of claims 30-39 under 103 (a) is withdrawn, however, the following 103 (a) Non-Final rejections are being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-38 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Cutson et al. (Physical Therapy, 1995, Vol. 75, No.5, pgs. 363-373) in view of Silvestrini (U.S. 4,132,791) and in further view of Kent (The Lancet, 2000, Vol. 355, pgs. 911-918).

Cutson et al. teaches that Parkinson's disease is a neurodegenerative disease characterized by cardinal signs such as tremors, bradykinesia, rigidity, and postural instability due to loss of dopamine which consequentially result in reduced excitatory motor cortex and occurrence of other symptoms including depression (see pg. 363, Introduction, left col., pg. 364, right col. last paragraph, and pg. 365, left and middle col.). Cutson et al. further teaches that L-dopa is the mainstay treatment but as dopamine does not cross the blood brain barrier, the levo-isomer (L-dopa) is typically given since it enters the central nervous system (CNS) and undergo enzymatic conversion to dopamine (see pg. 366, middle col.). However, given that L-dopa is rapidly metabolized peripherally before crossing into the brain, large amount of L-Dopa is generally necessitated; however, to avoid adverse effects with large amount of L-Dopa, the combination of carbidopa, a peripheral decarboxylase inhibitor that prevents peripheral conversion of L-dopa, with Levodopa or the composition Sinemet (i.e. tablet composition of carbidopa and levodopa; instant claim 38) is the commonly form used to

date containing 50 mg of carbidopa and 200 mg of levodopa or 25 mg of carbidopa and 100 mg of levodopa (i.e. Sinemet CR) (instant claims 33-35; see L-Dopa section, pg. 366, middle col.). Importantly, Cutson et al. teaches that the effects of dopamine agonists such as Amantadine are mostly on the symptom of rigidity (see pg. 368, Dopamine agonist section, left col.).

Cutson et al. does not specifically teach a method of treating Parkinson disease comprising a composition comprising 2-[3-[4[-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4,-triazol-3(4H)-one (i.e. nefazodone). Similarly, Cutson et al. does not teach a method comprising administered said composition in two to three single doses or in one or more single doses of about 100 mg to about 200 mg.

Silvestrini teaches treatment of tremors in Parkinsonism by administering trazodone and etoperidone in the range of 25 mg to 100 mg three times a day (see abstract). Silvestrini further teaches that Parkinson disease is characterized by tremors and muscular hypertonia, and administration of the psychotropic agents, trazodone and etoperidone, will reduce the two main components of Parkinson's disease (see col. 1, lines 10-62). Moreover, Silvestrini teaches that dopaminergic or adrenergic compounds, such as L-Dopa or dopamine agonists such as Amantadine, are mostly effective against rigidity and in fact may produce tremors and side effects and therefore suggest that tremors and rigidity have a different neurotransmitter basis (see col. 2, lines 25-30). Silvestrini demonstrated that adrenergic substances such as clonitidine

induce tremors and are inhibited by trazodone and etoperidone (see col. 2, lines 31-56). Likewise, Silvestrini demonstrated that trazodone or etoperidone pre-administration followed by nicotine administration abrogated nicotine-induced tremors (see col. 3, lines 4-7). Since trazodone and etoperidone have potent adrenolytic action, Silvestrini concluded that the anti-tremor activity of trazodone and etoperidone are due to the fact that they are adrenolytic agents (see col. 4, lines 50-58 and col. 4, table II). Additionally, Silvestrini teaches that the dosage of trazodone employed in various studies was 50 mg capsule three times daily (instant claims 36-37; see col. 5, lines 1-5).

Kent teaches new antidepressant with greater specificity including nefazodone (see abstract, pg. 911). Importantly, Kent teaches that nefazodone is structurally related to trazodone (see pg. 912, left col. paragraph 1). Moreover, Kent teaches that nefazodone was developed to improve the pharmacological characteristics of the earlier antidepressant trazodone (see pg. 912, right col. paragraph 1). Moreover, the recommended doses of nefazodone is 200 mg per day (i.e. single dose) or 100 mg twice a day (i.e. multiple single dose) wherein the dose can range from 300-600 mg daily (see pg. 912, right col. paragraph 2).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to substitute nefazodone into the composition of Silvestrini since trazodone and nefazodone are functional equivalents and are structurally similar. Moreover, it is considered that one of ordinary skill in the art at the time of the invention

was made would have found it obvious to substitute the nefazodone of Kent for the trazodone of Silvestrini given that the substitution of one known element for another would have yielded predictable results.

Additionally, one of ordinary skill in the art at the time of the invention would have bound it obvious to combine the now modified composition of Silvestrini with the composition of Cutson et al. since Silvestrini teaches that L-Dopa is mostly effective against rigidity and not tremor symptoms. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Thus, given that Cutson et al. teaches a method of treating Parkinson disease with L-Dopa, and Silvestrini teaches that L-Dopa is not effective against rigidity and suggests the use of trazodone and/or etoperidone for anti-tremor activity, and Kent teaches that nefazodone is structurally similar to trazodone and was developed to improve over the adverse effects of trazodone, one of ordinary skill would have been motivated to substitute nefazodone for trazodone as taught by Kent, and combine the methods of Silvestrini and Cutson et al. with the reasonable expectation of providing a successful method of treating Parkinson disease that is efficacious in alleviating rigidity and efficacious in suppressing tremors.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cutson et al. (Physical Therapy, 1995, Vol. 75, No.5, pgs. 363-373) in view of Silvestrini (U.S. 4,132,791) and in further view of Kent (The Lancet, 2000, Vol. 355, pgs. 911-918) as applied to claims 32-38 above and in further view of Ross et al. (JAMA. 2000, Vol. 283, No. 20, pgs. 2674-2679).

The Cutson, Silvestrini and Kent references are as discussed above and incorporated by reference herein. However, Cutson, Silvestrini and Kent do not address the addition of caffeine or acetyl salicylic acid or combinations thereof in the aforementioned method of treatment.

Ross et al. teaches that no treatment exist to slow the progression of Parkinson Disease (see pg. 2674, left col. paragraph 1). Ross et al. further teaches that coffee intake has been inversely associated with PD occurrence but found that PD incidence decline consistently with increased amount of caffeine intake (instant claim 39; see abstract-Results, fig. 1, table 2, and figure 2). This reduction in incidence is taught by Ross et al. to be due to possibly caffeine being neuroprotective or counteracting aging related neurodegeneration, or the antagonistic effect of caffeine on adenosine A2 receptors which improves motor deficits as seen in animals, or the fact that caffeine can decrease clinical expression of Parkinsonism by increasing dopaminergic tone (see pg. 2678, middle col.).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to add caffeine into the method of Cutson and Silvestrini since Ross et al. teaches that caffeine may play a role in slowing aging-induced neurodegeneration. Given that Cutson et al. teaches a method of treating Parkinson disease with L-Dopa, and Silvestrini teaches that L-Dopa is not effective against rigidity and suggests the use of trazodone and/or etoperidone for anti-tremor activity, and Kent teaches that nefazodone is structurally similar to trazodone and was developed to improve over the adverse effects of trazodone, and Ross et al. teaches that caffeine may slow aging-induced neurodegeneration, one of ordinary skill would have been motivated to substitute nefazodone for trazodone as taught by Kent, and combine the methods of Silvestrini and Cutson et al. and add caffeine with the reasonable expectation of providing an enhanced method of treating Parkinson disease that is efficacious in alleviating rigidity and tremors and a method efficient in slowing down the progression of Parkinson's disease.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

05/15/2008

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617